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Journal club

EOLIA trial: the future of extracorporeal membrane oxygenation in acute respiratory distress syndrome therapy?

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Commentary on:

Combes A, *et al*. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378: 1965–1975.

Context

Severe acute respiratory distress syndrome (ARDS) has very high mortality despite advances in the understanding of lung protective ventilation and interventions that improve survival [1]. Extracorporeal membrane oxygenation (ECMO) can allow for the gaseous exchange to happen outside the body and lungs can be ventilated with minimal mechanical stress. The first randomised controlled trial for the use of ECMO in ARDS showed that survival was no different with use of ECMO than conventional ventilation; however, ECMO use had complications including cannulation-associated bleeding and infection [2]. Morris *et al*. [3] studied extracorporeal carbon dioxide removal ($ECCO_2R$) with low frequency ventilation in patients with ARDS and compared it to conventional mechanical ventilation. This study suffered from technical difficulties as the ECMO/$ECCO_2R$ technology was very primitive and invasive. ECMO resurfaced during the H1N1 outbreak in 2009. A number of centres around the world provided nonrandomised survival data in patients on ECMO in response to this outbreak [4–6]. Peek *et al*. [7] studied ECMO for severe ARDS and showed higher survival rates in patients that were referred to ECMO centres as compared with past studies, but not substantially better than conventional management. The EOLIA (ECMO to rescue acute lung injury in severe ARDS) study [8] aims to answer the question: does early application of ECMO in severe ARDS improve mortality?

Methods

This was a prospective, multi-centre randomised controlled trial that involved centres in 16 countries. The trial was designed as a group sequential analysis with data analysed after randomisation of every 60 participants; stopping rules were predefined using the two triangle method. The trial could be stopped due to safety (due to excessive mortality in the ECMO arm), efficacy or futility (if unlikely to reach a definitive result). The trial was designed to have a power of 80% and alpha level of 5% to detect an absolute risk reduction of 20%. It was hypothesised that the mortality would be 60% in the conventional arm and 40% in the ECMO arm. Mortality at 60 days was the primary outcome measured.

The patients included had severe ARDS (per the American European Consensus Definition 1994), were intubated for <7 days, and despite optimal

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In the EOLIA trial, early use of ECMO did not significantly improve mortality at 60 days in patients with severe ARDS, but when used as a rescue modality ECMO might help improve survival
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mechanical ventilation and use of appropriate or rescue therapies (including paralysis, proning, inhaled nitric oxide) still had severe hypoxaemia or persistent severe respiratory acidosis. Patients with age <18 years, BMI >45 $kg \cdot m^{-2}$, irreversible neuronal injury, cardiac failure requiring venoarterial ECMO (VA ECMO), chronic respiratory failure (requiring home O_2) or cancer with life expectancy <5 years were excluded.

Patients meeting eligibility criteria were randomised to venovenous ECMO (VV ECMO) or conventional mechanical ventilation. Patients randomised to the ECMO arm could be on mechanical ventilation with settings adjusted to keep arterial oxygen tension (Pa_{O_2}) at 65–90 mmHg. Patients in the control arm were on volume assist control with inspiratory oxygen fraction (F_{IO_2}) at 21–100%, positive end-expiratory pressure (PEEP) adjusted to keep plateau pressure 28–30 cmH_2O. There were parameters for ventilator settings in both the control and ECMO arm with all participating centres undergoing training before the start of the trial. Patients in the control arm could be crossed over to the ECMO arm if arterial oxygen saturation (Sa_{O_2}) was <80% for >6 h despite use of all the rescue therapies at the treating physician's discretion.

While the primary outcome studied was mortality at 60 days, other outcomes of interest that were monitored included mortality at 90 days, median length of stay in the intensive care unit (ICU), median length of stay in the hospital, median days free from ventilation, and treatment failure. Treatment failure was defined as cross over to ECMO or death in the control arm, and death in the ECMO arm. The adverse effects observed were thrombocytopenia (defined as platelets <20000 mm^{-3}), severe bleeding events (requiring ≥1 packed red blood cell transfusion), ischaemic stroke, pneumothorax and rate of infections.

Main results

Over 6 years, a total of 1015 patients were assessed and 249 underwent randomisation. 124 patients were randomised to the ECMO arm and 125 were randomised to the control arm. 728 were excluded for various reasons, but most were excluded for intubation >7 days or being on ECMO prior to randomisation. Because no significant group difference in mortality at 60 days was found during the fourth interim analysis with just over 240 patients enrolled, trial recruitment was stopped in accordance with the prespecified rules noted above.

Patients in both arms were well matched. 121 patients out of the 124 in the ECMO arm received ECMO. Two patients passed away before they could receive ECMO and one improved before getting ECMO. In the control arm, 28% (35 out of 125) crossed over to ECMO at a median of 4 days (IQR 1–7 days).

In the intention-to-treat analysis, mortality at 60 days was 35% (44 out of 124) in the ECMO arm and 46% (57 out of 125) in the control arm; a relative risk of 0.76 (95% CI 0.55–1.04) with p-value of 0.09. This meant an absolute risk reduction of 11% in the ECMO arm, but this did not reach statistical significance. Treatment failure (defined as death in the ECMO arm and crossover to ECMO, or death in the control arm) at 60 days was 35% in the ECMO arm and 58% in the control arm; a relative risk of 0.62 (95% CI 0.47–0.82) with p-value <0.001. Median length of stay in the ICU and hospital was higher in the ECMO arm (median of 5 and 18 days, respectively). Ventilator-free days and days free of vasopressors and renal replacement therapy were also higher in the ECMO arm (median of 20, 9 and 32 days, respectively). Only 66% patients in the ECMO arm required proning while 90% in the control arm were proned. The 60 day mortality in the crossover patients was higher, 57% (20 out of 35) compared with the control arm, 41% (24 out of 90). In addition to severe hypoxia, patients who were crossed over also required higher vasopressor/inotropes and had worsening mixed respiratory and metabolic acidosis. In the supplemental analysis of the crossover data the hazard ratio for death within 60 days for the ECMO group compared to the control after adjusting for crossover with rank preserving structural failure time analysis (RPSFT), was 0.51 (0.24–1.02; p=0.055). Adverse effects like thrombocytopenia, bleeding events and cannula site infection were higher in ECMO group.

Commentary

The authors concluded that ECMO for severe ARDS showed no significant mortality benefit at 60 days as compared to conventional mechanical ventilation [8]. The trial was underpowered to answer the research question as it was stopped early due to futility (249 out of 331 recruited). The absolute risk reduction of 20% would not have been achieved even if the trial continued recruitment to a total sample size of 331 patients. To design a study to detect this difference a total of 624 patients would have been required. With the recruitment rate of EOLIA (0/0.58 patients/unit/month) and 100 participating sites, such a study would take 9 years [9].

The 28% crossover to ECMO may have skewed the results in the intention-to-treat analysis. In addition, adjusted crossover analysis did not distinguish between VA and VV ECMO as seven of the crossed over patients received VA ECMO. This has been addressed in a letter to the editor that pointed out the RPSFT analysis models used to analyse crossover can be less accurate if the crossover group receives the intervention for a similar duration as the group initially assigned to the intervention, as was the case here. In an as-treated analysis of the data, mortality was 40% in the ECMO arm and 42% in the control arm [10]. A different

view was discussed by Gattinoni *et al.* [9] who noted that the relative risk reduction would have increased to a significant value when analysing data using the likely decreased survival of the crossover group had they not been placed on ECMO.

This trial showed that ECMO is safe and not associated with significantly higher mortality than standard care. When used as a rescue modality ECMO can help improve survival in patients (15 out of 35 in the crossover arm) that would otherwise have probably died. Theoretically ECMO improves outcomes by reducing the stress of ventilation [11]. In the ECMO arm, tidal volume was reduced by almost half and respiratory rate was reduced by a quarter on the same PEEP level. That represents a significant reduction in mechanical stress from ventilation.

Implications for practice

EOLIA shows us that ECMO is safe and appropriate to use with no additional mortality than conventional therapy. A negative trial does not indicate that there is no role for ECMO in severe ARDS and some statistical and recruitment issues may have skewed the results [12]. While perhaps we should not be putting all severe ARDS patients on ECMO upon their presentation, consideration should still be given to using ECMO as a rescue modality as it may improve mortality in patients failing conventional and other rescue therapies for ARDS, as illustrated by the 15 crossover patients in this study who survived.

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Conflict of interest

None declared.

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